



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US00/02524</p> <p>(22) International Filing Date: 25 February 2000 (25.02.00)</p> <p>(30) Priority Data: 60/122,111 26 February 1999 (26.02.99) US</p> <p>(71) Applicant (for all designated States except US): NITROMED, INC. [US/US]; 12 Oak Park Drive, Bedford, MA 01730 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): GARVEY, David, S. [US/US]; 10 Grand Hill Drive, Dover, MA 02030 (US). LETTS, L., Gordon [AU/US]; 12 Abbott Road, Dover, MA 02030 (US). TAM, Sang, William [US/US]; 148 Pine Street, Dover, MA 02030 (US). WANG, Tiansheng [CN/US]; 2 Dumbar Way, Concord, MA 01742 (US). RICHARDSON, Stewart, K. [GB/US]; 55 Autumn Drive, Tolland, CT 06084 (US).</p> <p>(74) Agent: GRIEFF, Edward, D.; Hale and Dorr LLP, 1455 Pennsylvania Avenue, N.W., Washington, D.C. 20004 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	

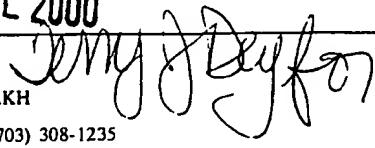
(54) Title: **NITROSATED AND NITROSYLATED PROTON PUMP INHIBITORS, COMPOSITIONS AND METHODS OF USE**

(57) Abstract

The present invention describes novel nitrosated and/or nitrosylated proton pump inhibitor compounds, and novel compositions comprising at least one proton pump inhibitor compound that is optionally substituted with at least one NO and/or NO₂ group, and, optionally, at least one compound that donates, transfers or releases nitric oxide, stimulates endogenous synthesis of nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor or is a substrate for nitric oxide synthase, and/or at least one nonsteroidal antiinflammatory drug, selective COX-2 inhibitor antacid, bismuth-containing reagent, acid-degradable antibacterial compound, and mixtures thereof. The present invention also provides methods for treating and/or preventing gastrointestinal disorders; facilitating ulcer healing; decreasing the recurrence of ulcers; improving gastroprotective properties, anti-*Helicobacter pylori* properties or antacid properties of proton pump inhibitors; decreasing or reducing the gastrointestinal toxicity associated with the use of nonsteroidal antiinflammatory compounds; treating *Helicobacter pylori* and viral infections. The compounds and/or compositions of the present invention can also be provided in the form of a pharmaceutical kit.

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A. CLASSIFICATION OF SUBJECT MATTER		
IPC(7) : A61K 31/437, 31/4184, 31/4439 ; C07D 471/04, 401/12, 235/28 US CL : 514/303, 338, 395 ; 546/118, 273.7 ; 548/307.1 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/303, 338, 395 ; 546/118, 273.7 ; 548/307.1		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE, APS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,629,305 A (EEK et al) 13 May 1997 (13.05.97), claims 1-19.	1-78 (in part)
A	US 5,599,794 A (EEK et al) 04 February 1997 (04.02.97), claims 1-2.	1-78 (in part)
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: *A* document defining the general state of the art which is not considered to be of particular relevance *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *E* earlier document published on or after the international filing date *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *&* document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
25 APRIL 2000	05 JUL 2000	
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer CHANA AULAKH  Telephone No. (703) 308-1235	

Form PCT/ISA/210 (second sheet) (July 1998) *

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-78(In Part)

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

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BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

- I. Claims 1-78 (in part) directed to, A proton pump inhibitor compound represented by compounds of formula (I), classified in class 546, subclass 118+.
- II. Claims 1-78 (in part) directed to, A proton pump inhibitor compound represented by compounds of formula (II), classified in class 546, subclass 152+.
- III. Claims 1-78 (in part) directed to, A proton pump inhibitor compound represented by compounds of formula (III), classified in class 544, subclass 242+.
- IV. Claims 1-78 (in part) directed to, A proton pump inhibitor compound represented by compounds of formula (IV), classified in class 548, subclass 126+.
- V. Claims 1-78 (in part) directed to, A proton pump inhibitor compound represented by compounds of formula (V), classified in class 546, subclass 255+.
- VI. Claims 1-78 (in part) directed to, A proton pump inhibitor compound represented by compounds of formula (VI), classified in class 548, subclass 303.1+.
- VII. Claims 1-78 (in part) directed to, A proton pump inhibitor compound represented by compounds of formula (VII), classified in class 546, subclass 121+.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:
There is no common core which in the Markush Practice, is a significant structural element shared by all of the alternatives; see PCT Administrative Instructions Annex B Part I (f) (i) (B) (1).